UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,127	11/06/2006	Peter Anthony Campochiaro	010804-22690600	2577

78018 7590 03/02/2009

MDIP LLC
POST OFFICE BOX 2630
MONTGOMERY VILLAGE, MD 20886-2630

EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
03/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,127	CAMPOCHIARO ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *4, 7-20, and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,21 and 27-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of record has changed. Please direct all further correspondence to Scott Long whose phone number is 571-272-9048.

Election/Restrictions

Examiner acknowledges the election, without traverse, of Group II directed to a method of treating retinal edema with a nucleic acid encoding endostatin, in the reply filed on 23 August 2008. In addition, the examiner acknowledges the election, without traverse, of the species of vector, lentivirus. The applicant has indicated that claims 1-3, 5, 6, 21 and 27-42 read on the elected species.

Additionally, the examiner acknowledges the applicant's statement that claims 24-26 were incorrectly included in Group II and should be included in Group III. The current examiner appreciates this statement by the applicant and hereby withdraws claims 24-26 from examination.

The previous examiner had used WO02/30982 to show lack of a special technical feature and thereby justify a lack of unity restriction. In the applicant's Remarks, the applicant states, the "publication teaches a combination treatment rather than use of endostatin alone and there is no mention of treating ocular edema. Hence, that published PCT application does not anticipate the claimed inventions." The examiner is not sure whether this is a traversal of the restriction requirement or merely an opinion regarding a potential "anticipation" rejection. To the extent that it might be a traversal, the examiner finds this argument unpersuasive. The previous examiner was

correct in interpreting the instant claim language as open and therefore permitting administration of more than merely endostatin for treating eye diseases having retinal detachment or retinal edema as symptoms. Furthermore, independent claim 1 does not specify what agent is responsible for "effecting an increase in the amount of an endostatin in ocular tissues of an individual."

Because the applicant has not explicitly stated that the election was "with traverse," the examiner considers the election to be "without traverse." Because no argument for the traversal was provided by applicant, thus the traversal is non-persuasive and the restriction is made final.

Claim Status

Claims 1-42 are pending. However, claims 4, 7-20, and 22-26 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 43-48 are cancelled. Claims 1-3, 5, 6, 21 and 27-42 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The new oath or declaration, having the signatures of all inventors, received on 6 November 2006 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 21 February 2006 consisting of 1 sheet(s) are in compliance with 37 CFR 1.97. Several references cited on the IDS were not submitted to the USPTO. Therefore, they were not considered. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit under 35 USC 371 as a National Stage entry of PCT/EP03/09497 (filed 27 August 2003). This application also claims benefit from provisional U.S. Application No. 60/406,470, filed 28 August 2002. The instant application has been granted the benefit date, 28 August 2002, from the application 60/406,470.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5, 6, 27-31, 36-42 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-3, 27-28, 30-32, 38-41, 45, 51-62 of copending Application No. 10/080797. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The instant application is directed to treating retinal edema, while the copending application, 10/080797, is directed to treating a large genus of diseases for which retinal edema is a symptom. Both applications use gene therapy methods to deliver the same SEQ ID NO encoding human endostatin. Accordingly, the claims of 10/080797 are obvious over the instant claims.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 1-3, 5, 6, 31, 36, 41 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 9, 11, 16 of copending Application No. 10/529428. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The instant application is directed to treating retinal edema, while the copending application, 10/529428, is directed to treating the retina of a subject in need of such delivery encompassing a large genus of diseases for which retinal edema is a symptom. Both applications use gene therapy methods to deliver nucleic acids encoding human endostatin. Application 10/529428 recites periocular injection in claim 1, while the instant application recites periocular injection delivery in dependent claim 41. Accordingly, the claims of 10/529428 are obvious over the instant claims.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 1, 5, 6, and 31 are provisionally rejected on the ground of nonstatutory double patenting over claims 52-56, and 59 of copending Application No. 10/910293. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The instant application is directed to treating retinal edema, while the copending application, 10/910293, is directed to treating the retina of a subject in need of such delivery encompassing a large genus of diseases for which retinal edema is a symptom. Both applications use gene therapy methods to deliver nucleic acids encoding human endostatin. The claims of Application 10/910293 are more generic than those of the instant application, however, the claims of 10/910293 recite Markush groups which encompass the specific embodiment of the instant claims directed to methods of treating retinal edema with a

lentivirus encoding endostatin. Accordingly, the claims of 10/910293 are obvious over the instant claims.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step/element is: the method step or agent which is capable of "effecting an increase in the amount of an endostatin in ocular tissues of an individual." The phrase "effecting an increase" does not clearly indicate the metes and bounds of the claimed method. In other words, how is the "effecting" being accomplished?

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 33 recites the phrase "at least about 300 ng/ml." MPEP 2173.05(b) indicates that the phrase "at least about" is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 6, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Leboulch et al (WO99/26480) and as evidenced by Chu et al. (Drug Development Research. 2008; 69:1-14).

Claim 1 is directed to a method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount. Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which expresses the anti-angiogenic polypeptide endostatin, wherein expression of endostatin in the patient inhibits angiogenesis in the vicinity of the retina (claim 33). Chu et al. indicates diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema (Introduction and page 7, col.2 to page 8, col.1). So, while treating diabetic retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema. Regarding the limitations directed to "to a retinal edema-inhibiting effective amount," the specification

does not specifically define this phrase. However, the specification provides a definition for to a "retinal disorder inhibiting effective amount" and indicates that this amount is determined by observation of endostatin's effect on retinal vascular permeability, retinal thickness or degree of retinal detachment. The specification also indicates "[a] therapeutically effective dose of an active agent can be estimated either in cell culture assays...or in animal models" (page 7, parag.5). The claimed amount is not quantitatively exact, but is determined empirically. Therefore, the examiner concludes that Leboulch et al. provides such an amount.

Claim 2 is directed to the method of claim 1 wherein the endostatin is a polypeptide with the amino acid sequence set forth in SEQ ID NO:1. SEQ ID NO:1 encodes human endostatin. Leboulch et al teach that their inventions use the anti-angiogenic polypeptide, human endostatin.

Claim 3 is directed to the method of claim 1, wherein the endostatin is a polypeptide fragment, derivative, or variant of the amino acid sequence set for the in SEQ ID NO:1. SEQ ID NO:1 encodes human endostatin. Leboulch et al teach that their inventions use the anti-angiogenic polypeptide, human endostatin. The specification indicates that endostatin fragments can be a full-length endostatin (page 3, parag.2).

Claim 5 is directed to the method of claim 1, wherein the increase is effected by causing endostatin to be produced within an individual. Leboulch et al teach gene therapy methods in humans.

Claim 6 is directed to the method of claim 5, wherein the increase is effected by administering an effective amount of a viral vector comprising and endostatin-encoding nucleic acid to the individual. Leboulch et al. teach "the nucleic acid molecule preferably constitutes a portion of a viral vector, which can...[be] administered to the patient so that...cells are infected" (page 2, lines 14-18).

Claim 27 is directed to the method of claim 6, wherein the endostatin-encoding nucleic acid has the sequence set forth in SEQ ID NO:2. The specification indicates that SEQ ID NO:2 encodes SEQ ID NO:1, which is the sequence for human endostatin. Leboulch et al teach that their inventions use nucleic acids encoding the human endostatin polypeptide.

Accordingly, Leboulch et al. anticipated the instant claims.

Claims 1, 5, 6 are rejected under 35 U.S.C. 102(a) as being anticiapted by Mori et al. (American Journal of Pathology. July 2001; 159(1): 313-320).

Claim 1 is directed to a method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount. Mori et al. teach gene therapy methods for inhibiting neovascularization in the retina comprising administering an adenoviral vector having an endostatin gene. Mori et al. demonstrate that the endostatin gene is expressed in a mouse model. Mori et al. show neovascularization is inhibited at the

choroidal/retinal interface. The art recognizes that neovascularization in the retina is a cause of edema.

Claim 5 is directed to the method of claim 1, wherein the increase is effected by causing endostatin to be produced within an individual. Mori et al. demonstrate that the endostatin gene is expressed in a mouse model.

Claim 6 is directed to the method of claim 5, wherein the increase is effected by administering an effective amount of a viral vector comprising and endostatin-encoding nucleic acid to the individual. Mori et al. teach gene therapy methods for inhibiting neovascularization in the retina comprising administering an adenoviral vector having an endostatin gene.

Accordingly, Mori et al. anticipated the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 31, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107).

Claim 1 is directed to a method for the treatment of retinal edema in an individual afflicted with retinal edema, comprising effecting an increase in the amount of endostatin in ocular tissues of an individual afflicted with retinal edema to a retinal edema-inhibiting effective amount. Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which expresses the anti-angiogenic polypeptide endostatin, wherein expression of endostatin in the patient inhibits angiogenesis in the vicinity of the retina (claim 33). A skilled artisan is aware that diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema. So, while treating diabetic

retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema. Regarding the limitations directed to "to a retinal edema-inhibiting effective amount," the specification does not specifically define this phrase. However, the specification provides a definition for to a "retinal disorder inhibiting effective amount" and indicates that this amount is determined by observation of endostatin's effect on retinal vascular permeability, retinal thickness or degree of retinal detachment. The specification also indicates "[a] therapeutically effective dose of an active agent can be estimated either in cell culture assays...or in animal models" (page 7, parag.5). The claimed amount is not quantitatively exact, but is determined empirically. Therefore, the examiner concludes that Leboulch et al. provides such an amount.

Claim 5 is directed to the method of claim 1, wherein the increase is effected by causing endostatin to be produced within an individual. Leboulch et al teach gene therapy methods in humans.

Claim 6 is directed to the method of claim 5, wherein the increase is effected by administering an effective amount of a viral vector comprising and endostatin-encoding nucleic acid to the individual. Leboulch et al. teach "the nucleic acid molecule preferably constitutes a portion of a viral vector, which can...[be] administered to the patient so that...cells are infected" (page 2, lines 14-18).

Claim 31 is directed to the method of claim 6, wherein the viral vector is a lentiviral vector. Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34).

Claim 36 is directed to the method of claim 31, wherein the lentiviral vector is a bovine immunodeficiency viral (BIV) vector. Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34).

Claim 37 is directed to the method of claim 36 wherein the bovine immunodeficiency viral vector is administered intraocularly. Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection. Therefore, Poeschla et al suggest intraocular injection of the BIV vector.

Leboulch et al. does not teach using lentiviral vectors, and particularly Bovine Immunodeficiency Virus (BIV) vectors in their method of treating retinal edema with nucleic acids encoding human endostatin.

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Leboulch et al. and Poeschla et al. to

treat retinal edema using lentiviral vectors such as Bovine Immunodeficiency Virus (BIV) comprising the gene for human endostatin.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34).

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Leboulch et al. and Poeschla et al. because each of the cited art provides examples of successful gene transfer.

Therefore the method as taught by Leboulch et al in view of Poeschla et al. would have been *prima facie* obvious over the method of the instant application.

Claims 21, 28-30 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) as applied to claims 1, 5, 6, 31, and 36 above, and further in view of Brandt et al. (US-6106826).

The teachings of claims 1, 5, 6, 31, and 36 are described above in the obviousness rejection over Leboulch et al. in view of Poeschla et al.

In summary, Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which expresses the anti-angiogenic polypeptide endostatin, wherein expression of endostatin

in the patient inhibits angiogenesis in the vicinity of the retina (claim 33). A skilled artisan is aware that diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema. So, while treating diabetic retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema.

Leboulch et al. does not teach using lentiviral vectors, and particularly Bovine Immunodeficiency Virus (BIV) vectors, in their method of treating retinal edema with nucleic acids encoding human endostatin.

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors…for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

Claim 21 is directed to the method of claim 6, wherein the vector is admininstered in an amount from about 10^8 plaque forming units to about 10^{14} plaque forming units. Brandt et al. teach method of gene therapy for treating retinal diseases (abstract). Brandt et al. also teaches "[i]n the human eye it should be possible to give at least 100µl per injection, which is equivalent to 10^8 to 10^9 PFU per injection" (col.9, lines 9-10).

Claims 28-30 are directed to the method of claim 6 wherein the viral vector is administered intraocularly (claim 28), subretinally (claim 29), and intravitreally (claim

30). Brandt et al. teach subretinal and intravitreal injection for treatment of ocular diseases. These methods encompass intraocular administration.

Claims 37-39 are directed to the method of claim 36 wherein the viral vector is administered intraocularly (claim 37), subretinally (claim 38), and intravitreally (claim 39). Brandt et al. teach subretinal and intravitreal injection for treatment of ocular diseases. These methods encompass intraocular administration.

Claim 40 is directed to the method of claim 6, wherein the increase is inducibly effected by the administration to the individual of a viral vector that can cause the production in the individual of an agent that will induce the expression of the endostatin-encoding nucleic acid. Brandt et al. suggest gene therapy methods of treating retinal diseases comprising viral vectors having inducible promoters operably linked to a therapeutic gene (abstract and col.2, line 56).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Leboulch et al. and Poeschla et al. and Brandt et al. to treat retinal edema using lentiviral vectors such as Bovine Immunodeficiency Virus (BIV) comprising the gene for human endostatin, using a variety of delivery methods including intraocular, subretinal and intravitreal injection. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of

the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a BIV delivery vector, and various methods of delivery to the retina) are taught by Leboulch or Poeschla or Brandt and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these three elements in a method of gene therapy for retinal edema.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, subretinal and intravitreal injections were know in the art of treating retinal diseases.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Leboulch et al. and Poeschla et al. and Brandt et al. because the cited art provides examples of successful gene delivery by subretinal and intravitreal injection.

Therefore the method as taught by Leboulch et al in view of Poeschla et al. and further in view of Brandt et al. would have been *prima facie* obvious over the method of the instant application.

Claims 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) as applied to

claims 1, 5, 6, 31, and 36 above, and further in view of Clark et al. (Exp. Opin. Ther. Patents. 2000; 10(4): 428-448).

The teachings of claims 1, 5, 6, 31, and 36 are described above in the obviousness rejection over Leboulch et al. in view of Poeschla et al.

In summary, Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which expresses the anti-angiogenic polypeptide endostatin, wherein expression of endostatin in the patient inhibits angiogenesis in the vicinity of the retina (claim 33). A skilled artisan is aware that diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema. So, while treating diabetic retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema.

Leboulch et al. does not teach using lentiviral vectors, and particularly Bovine Immunodeficiency Virus (BIV) vectors, in their method of treating retinal edema with nucleic acids encoding human endostatin.

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

Claims 41 is directed to the method of claim 36, wherein the bovine immunodeficiency viral vector is admininstered periocularly. Clark et al. is a review

article which describes various method of treating the eye with angiostatic agents. Clark et al. teach methods comprising periocular injection (page 4, col.2, 1st parag.). Clark et al. suggest administering endostatin to control angiogenesis (page 430, col.1). Clark et al. describe methods of treating diabetic retinopathy and diabetic macular edema (page 431, col.2).

Claim 42 is directed to the method of claim 6, wherein the viral vector is administered periocularly. As detailed above, Clark et al. teach methods comprising periocular injection (page 4, col.2, 1st parag.).

Clark et al. do not teach gene therapeutic methods.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Leboulch et al. and Poeschla et al. and Clark et al. to treat retinal edema using lentiviral vectors such as Bovine Immunodeficiency Virus (BIV) comprising the gene for human endostatin, and using a periocular delivery method. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a BIV delivery vector, and periocular injection as a method of delivering compounds for treating the retina) are taught by Leboulch or Poeschla or

Clark and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these three elements in a method of gene therapy for retinal edema.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, periocular injections were know in the art of treating retinal diseases.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Leboulch et al. and Poeschla et al. and Clark et al. because the cited art provides examples of successful gene delivery by subretinal and intravitreal injection.

Therefore the method as taught by Leboulch et al in view of Poeschla et al. and further in view of Clark et al. would have been *prima facie* obvious over the method of the instant application.

Claims 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leboulch et al (WO99/26480) in view of Poeschla et al. (US-6,555,107) as applied to claims 1, 5, 6, 31, and 36 above, and further in view of Mori et al. (American Journal of Pathology. July 2001; 159(1): 313-320).

The teachings of claims 1, 5, 6, and 31 are described above in the obviousness rejection over Leboulch et al. in view of Poeschla et al.

In summary, Leboulch et al. teach a method of treating a human patient suffering from diabetic retinopathy comprising administering a nucleic acid molecule which expresses the anti-angiogenic polypeptide endostatin, wherein expression of endostatin in the patient inhibits angiogenesis in the vicinity of the retina (claim 33). A skilled artisan is aware that diabetic retinopathy is characterized by neovasculaturization of the retina resulting in retinal edema. So, while treating diabetic retinopathy with nucleic acids encoding endostatin, Leboulch et al. are treating retinal edema.

Leboulch et al. does not teach using lentiviral vectors, and particularly Bovine Immunodeficiency Virus (BIV) vectors, in their method of treating retinal edema with nucleic acids encoding human endostatin.

However, Poeschla et al teach non-primate lentivirus vectors, including Bovine Immunodeficiency Virus (BIV) vectors are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, Poeschla et al teach methods of gene therapy comprising infecting a cell of the eye with a non-primate lentivirus capable of expressing a heterologous gene (col.33, line 6). Furthermore, Poeschla et al. teach methods of administration comprising injection.

Claims 32-35 are directed to methods of claim 31, wherein the lentiviral vector is administered in an amount effective to provide for expression of endostatin by the individual to result in a concentration of endostatin of up to 1000000 ng/ml (claim 32), at

least about 300 ng/ml (claim 33), about 300 ng/ml to about 3000 ng/ml (claim 34), or about 300 ng/ml to about 1500 ng/ml (claim 35) in the serum of the individual.

Mori et al. teach adenoviral vector gene therapy methods for treating diabetic retinopathy caused by neovascularization (page 313, col.1). Mori et al. teach that their adenoviral vectors express endostatin where serum levels of endostatin achieve 1740 ng/ml (page 318, col.2, parag.1). This serum level of expressed endostatin satisfies the range limitations of instant claims 32-35. While Mori et al. achieved this level using Adenoviral vectors, Mori et al. suggest "lentivirus vectors could be considered" as a substitute for the Adenoviral systems (page 319. col.1, parag.2).

Mori et al. do not specifically indicate their treatments are directed to treating retinal edema, since neovascularization of the choroidal layer leads to retinopathy, the examiner concludes a skilled artisan would consider this an obvious application. Furthermore, Mori et al. indicate that diabetic retinopathy is a target of their therapy.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Leboulch et al. and Poeschla et al. and Mori et al. to treat retinal edema using lentiviral vectors such as Bovine Immunodeficiency Virus (BIV) comprising the gene for human endostatin, such that the serum level of endostatin falls in the ranges encompassed by claims 32-35. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded

predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (gene therapy methods comprising administering the human endostatin gene for treating retinal edema, gene therapy methods comprising a BIV delivery vector, and serum expression of endostatin of 1470 ng/ml from viral vectors) are taught by Leboulch or Poeschla or Mori and further they are taught in various combinations and are shown to be used in gene therapy methods for the eye. It would be therefore predictably obvious to use a combination of these three elements in a method of gene therapy for retinal edema.

The person of ordinary skill in the art would have been motivated to make those modifications because Poeschla et al teach non-primate lentivirus vectors, including BIV, are "potential sources of safer lentiviral vectors...for therapeutic gene transfer" (col.2, lines 10-34). In addition, Mori et al. suggest substituting lentiviral vectors for their successful adenoviral system in the art of treating retinal diseases.

The skilled artisan would have had a reasonable expectation of success in combining the teachings of Leboulch et al. and Poeschla et al. and Mori et al. because the cited art provides examples of successful gene expression of endostatin to a serum level of 1470 ng/ml.

Therefore the method as taught by Leboulch et al in view of Poeschla et al. and further in view of Mori et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633